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X-ray analysis of podophyllotoxone–a lignan

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Abstract : The crystal structure of the title compound ($C_{22}H_{20}O_8$) has been determined by X-ray crystallographic techniques. The compound crystallizes into orthorhombic space group $P2_12_12_1$ with unit cell parameters a = 6.518(4), b = 12.154(6), c= 24.922(9)Å, Z = 4. The structure has been solved by direct methods and refined to R = 0.086 for 1081 observed reflections. The five-membered heterocyclic rings A and D exist in envelope conformation. The phenyl rings B and E are planar while ring C assumes a distorted sofa conformation. The dihedral angle between the phenyl ring E and rest of the molecule is 90.4(2)°. The molecules in the structure are linked together by intra- and intermolecular C-H . O contacts

Keywords X-ray crystallography, direct methods, lignan

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Introduction

The title compound, a lignan, was obtained by the extraction of powdered roots / rhizomes of podophyllum hexandrum (500 gm) with ethanol, followed by concentration under vacuum. The concentrated mass was poured into cold water (2000 ml). The semi solid dark brown coloured residue was extracted with EtOAc (6 × 250 ml). The combined dried extract after removal of solvent was then subjected to column chromatography when it gave five major fractions. The first fraction after repeated column chromatography and preparative TLC gave podophyllotoxone.

The chemical structure assigned to this compound on the basis of IR, UV, NMR and mass spectral data is shown in Figure 1.

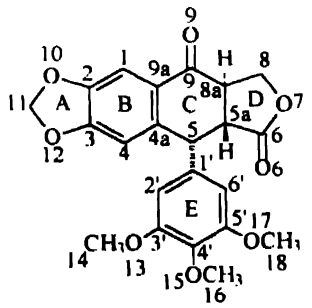

Figure 1. Chemical structure of Podophyllotoxone.

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2. Experimental

Colourless needle shaped single crystals of podophyllotoxone (m.p. 462-465K) were grown from methanol by slow evaporation at room temperature. Three-dimensional intensity data were collected on Enraf-Nonius CAD-4 diffractometer using MoKα radiation. The unit cell parameters were refined by the least-squares procedure. The data were corrected for Lorentz and polarization effects. Absorption and extinction corrections were not applied.

The structure has been solved by direct methods using SHELXS86 software [2]. All non-hydrogen atoms of the molecule were obtained from the E-map. Full-matrix least-squares refinement has been carried out using SHELXL93 software [3]. All H atom positions were calculated geometrically with U_{iso}(H) = 1.2 U_{eq} (parent atom). A riding model was used in their refinement (C-H = 0.92 – 0.97 Å). The final refinement cycle converged to R = 0.086 and $wR(F^2)$ = 0.224. Atomic scattering factors were taken from International Table for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 1.

Table 1. Crystal data and other experimental details.

Crystal description	Colourless needles
Chemical formula	$C_{22}H_{20}O_8$
Molecular weight	412 39
Cell parameters	a = 6 518(4), b = 12 154 (6) and c = 24.922(9) Å
Unit cell volume	1974 32 Å^3
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.387 Mg m^{-3}
No of molecules per unit cell (Z)	4
Radiation	MoKα
Wavelength (λ)	0 71073Å
Absorption coefficient (μ)	0 106mm^{-1}
Crystal size	0 35 × 0 20 × 0 20 mm
Refinement of unit cell	25 reflections, (5.9 < θ < 10.7°)
θ range for entire data collection	2 < θ < 25°
No of measured reflections	1710
No of unique reflections	1704
No of observed reflections	1081 [$F_0 > 4\sigma(F_0)$]
No of parameters refined	271
Final R-factor	0 086
wR (F^2)	0 224
Weight	$1/[\sigma^2(F_0^2)+(0.159P)^2+0.36P]$, Where $P=[F_0^2+2F_c^2]/3$
Goof (S)	1 002
Final residual electron density	$-0.37 < \Delta\rho < 0.35$eÅ^{-3}
(Δ/σ) max in the final cycle	0 020 (for U_{11} C9)

3. Results and discussion

The final atomic positions and equivalent isotropic displacement parameters for all the non-hydrogen atoms are presented in Table 2. Bond distances and bond angles for non-hydrogen atoms are listed in Table 3. An ORTEP view of the molecule with the atomic numbering scheme is shown in Figure 2[4] The geometry of the molecule has been calculated using the software PARST [5].

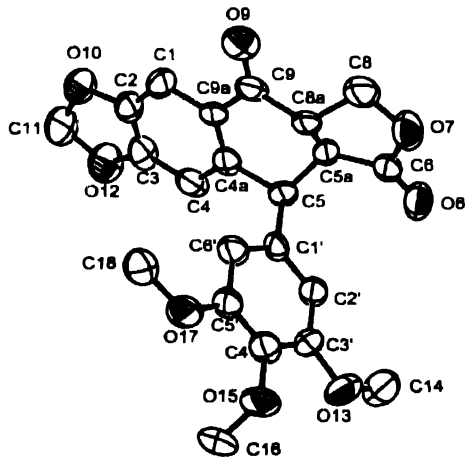

Figure 2. ORTEP view (50% probability level) of the title molecule

Table 2. Atomic coordinates and equivalent isotropic thermal parameters (Å^2) for non-hydrogen atoms (e.s.d.'s are given in parentheses)

atom				U*
C1	0 103(2)	0.028(1)	0.5513(3)	0.056(3)
C2	0 030(2)	-0.060(1)	0 5564(3)	0 056(3)
C3	0.217(2)	-0.053(1)	0.5785(3)	0.059(4)
C4	0.298(2)	0 047(1)	0.5988(3)	0 061(3)
C4a	0.167(2)	0.138(1)	0 5940(3)	0 047(3)
C5	0.259(1)	0.247(1)	0.6141(3)	0 046(3)
C5a	0.147(2)	0.338(1)	0 5836(3)	0 049(3)
C6	0.193(2)	0 457(1)	0.5920(3)	0 056(4)
O6	0 347(1)	0.502(1)	0 6041(3)	0 077(3)
O7	0.018(2)	0 513(1)	0 5784(3)	0 083(3)
C8	0.143(2)	0 440(1)	0.5641(4)	0 080(4)
C8a	0 076(2)	0.332(1)	0.5876(3)	0 053(3)
C9	0 157(2)	0.227(1)	0 5650(3)	0 048(3)
C9a	0.023(2)	0 132(1)	0.5712(3)	0 046(3)
O9	0 324(1)	0.222(1)	0 5434(2)	0 064(2)
O10	0 002(1)	-0 165(1)	0.5390(3)	0 078(3)
C11	0.157(2)	-0.225(1)	0.5596(5)	0 085(5)
O12	0.315(2)	-0 150(1)	0.5763(3)	0 090(3)
O13	0.515(1)	0 397(1)	0 7855(3)	0 075(4)
C14	0 687(2)	0 440(1)	0 7593(4)	0 076(4)
O15	0 215(1)	0 301(1)	0 8406(2)	0 076(3)
C16	0 325(2)	0 214(1)	0 8686(4)	0 081(4)
O17	0.065(1)	0 176(1)	0 7910(2)	0 065(2)
C18	0.213(2)	0.106(1)	0 7684(4)	0 069(4)
C1'	0.244(1)	0 259(1)	0 6752(3)	0 041(2)
C2'	0.388(1)	0 323(1)	0.7007(3)	0 049(3)
C3'	0 377(2)	0 337(1)	0.7566(3)	0 057(3)
C4'	0 223(2)	0 286(1)	0 7847(3)	0.058(3)
C5'	0 080(1)	0.223(1)	0.7600(3)	0 051(3)
C6'	0 091(1)	0 209(1)	0.7034(3)	0 052(3)

* $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i.a_j$.

The bond distance and bond angles are in agreement with some related structures [6-10]. The phenyl rings B and E show normal geometries. The phenyl ring B is perfectly planar with an average deviation of 0.001(9) Å. Ring E is also planar with an average deviation of 0.006(9) Å. The five-membered heterocyclic rings A and D exist in envelope conformation. The asymmetry parameters for rings A and D are : ΔC_s (C11) = 0.59 and ΔC_s (C8a) = 5.09, respectively [11]. Ring C adopts distorted sofa conformation with asymmetry parameter ΔC_s (C5a) = 9.4

Table 3. Selected bond distances (Å) and bond angles (°) for non-hydrogen atoms (e.s.d's are given in parentheses).

C1-C2	1.38(1)	C8a-C9	1.50(1)
C1-C9a	1.45(1)	C9-C9a	1.46(1)
C2-C3	1.34(2)	C9-O9	1.21(1)
C2-O10	1.36(1)	O10-C11	1.37(2)
C3-C4	1.41(1)	C11-O12	1.43(2)
C3-O12	1.34(1)	O13-C14	1.39(1)
C4-C4a	1.41(1)	O13-C3'	1.37(1)
C4a-C5	1.53(1)	O15-C16	1.45(1)
C4a-C9a	1.37(2)	O15-C4'	1.41(1)
C5-C5a	1.53(1)	O17-C18	1.40(1)
C5-C1'	1.53(1)	O17-C5'	1.35(1)
C5a-C6	1.50(1)	C1'-C2'	1.38(1)
C5a-C8a	1.46(1)	C1'-C6'	1.36(1)
C6-O6	1.19(2)	C2'-C3'	1.40(1)
C6-O7	1.37(2)	C3'-C4'	1.37(1)
O7-C8	1.42(2)	C4'-C5'	1.35(1)
C8-C8a	1.51(1)	C5'-C6'	1.42(1)
C2-C1-C9a	114(1)	C8a-C9-C9a	115(1)
C1-C2-C3	124(1)	C9a-C9-O9	123(1)
C3-C2-O10	109(1)	C4a-C9a-C9	123(1)
C2-C3-O12	111(1)	C1-C9a-C4a	121(1)
C2-C3-C4	123(1)	C2-O10-C11	105(1)
C5a-C6-O6	131(1)	O10-C11-O12	108(1)
C3-C4-C4a	115(1)	C3-O12-C11	104(1)
C4-C4a-C9a	123(1)	C14-O13-C3'	119(1)
C6-C5a-C8a	104(1)	C16-O15-C4'	111(1)
C5-C4a-C9a	123(1)	C18-O17-C5'	121(1)
C4a-C5-C1'	112(1)	C5-C1'-C6'	121(1)
C4a-C5-C5a	106(1)	C5-C1'-C2'	118(1)
C5a-C5-C1'	113(1)	C2'-C1'-C6'	121(1)
C5-C5a-C6	122(1)	C1'-C2'-C3'	119(1)
C5a-C6-O7	106(1)	C2'-C3'-C4'	119(1)
C6-O7-C8	111(1)	C3-C4'-C5'	122(1)
O7-C8-C8a	104(1)	C5a-C8a-C8	103(1)
C5a-C8a-C9	112(1)	C4'-C5'-C6'	119(1)
C8a-C9-O9	122(1)	C1'-C6'-C5'	119(1)
O6-C6-O7	122(1)		

The dihedral angle between the phenyl ring E and the rest of the molecule is 90.4(2)° which shows that this ring is held at right angles to the rest of the molecule consisting of rings A-D. This is also confirmed by the value of torsion angle C5a-C5-C1'-C6' = 92(1)°. Molecular packing in the unit cell down *a*-axis is depicted in Figure 3. Intra- and intermolecular C-H...O interactions which contribute to the stability of the crystal structure is given in Table 4.

Structure Factors Data have been deposited at the Editorial Office of the Journal.

Table 4. Geometry of intra- and intermolecular C-H ..O interactions.

X-H...*Y*	*X*...*Y*(Å)	H ..*Y*(Å)	*X*-H.. *Y*(o)
C2'-H2'.. O6	3.26(1)	2.78(1)	113(1)
C5-H5.. O9(ii)	3.25(1)	2.35(1)	153(1)
C5a-H5a ..O9(iii)	3.25(1)	2.29(1)	167(1)
C8-H82...O6(iii)	3.55(2)	2.59(2)	168(1)
C11-H112...O10(iv)	3.57(2)	2.68(2)	152(1)
C18-H181 . O6(v)	3.53(1)	2.68(1)	148(1)

Symmetry codes (i) $x+1, y, z$ (ii) $x+1/2, -y+1/2, -z+1$
(iii) $x-1, y, z$ (iv) $x+1/2, -y-1/2, -z+1$
(v) $-x, y-1/2, -z+1/2+1$

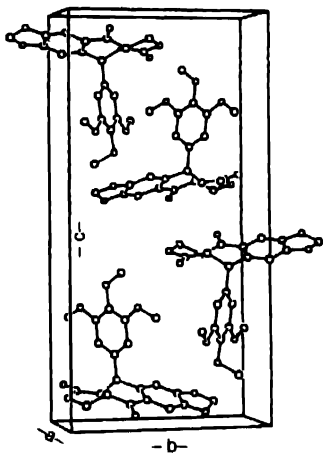

Figure 3. Packing diagram viewed down the *a*-axis

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